ART 34 AMDT

We claim:

Sub A3

1. A method of parallel analysis of biological specimens, comprising:

obtaining a plurality of donor specimens;

placing each donor specimen in an assigned location in a recipient array;

obtaining a plurality of copies of the recipient array in a manner that each copy contains a plurality of donor specimens that maintain their assigned locations;

performing a biological analysis of each copy; and

comparing the results of the biological analysis in corresponding assigned locations of different copies to determine if there are correlations between the results of the biological analysis at each assigned location.

2. The method of claim 1, wherein the donor specimen is obtained by boring an elongated sample from the donor specimen, which is placed in the assigned location in the recipient array.

3. The method of claim 1, wherein the donor specimen is from a tumor.

4. The method of claim 1, wherein the donor specimen is from a population of cells.

5. The method of claim 3, wherein the donor specimen is from a hematological or cytological preparation.

6. The method of claim 1, wherein placing the donor specimen in an assigned location in the recipient array comprises forming an elongated receptacle in a donor block, obtaining an elongated donor specimen, and placing the elongated donor specimen in the elongated receptacle of the recipient block, and obtaining a plurality of copies comprising sectioning the array transverse to the elongated donor specimen.

7. The method of claim 6, wherein the elongated donor specimen is placed in a receptacle having a cross-sectional size and shape complementary to a cross-sectional size and shape of the elongated donor specimen.

8. The method of claim 7, wherein forming the elongated receptacle comprises forming a cylindrical bore in the recipient block, and the donor specimen is obtained by boring a cylindrical tissue specimen from a donor block, wherein a diameter of the elongated receptacle is substantially the same as a diameter of the donor specimen.

Sub A4

9. The method of claim 1, further comprising associating a clinical or laboratory characteristic, or both, with each assigned location in the recipient array.

10. The method of claim 1 wherein performing the biological analyses comprises performing a different biological analysis on each copy.

11. The method of claim 10, wherein the different biological analyses are selected from the group consisting of at least an immunological analysis and a nucleic acid hybridization.

Sub A5> 12. The method of claim 10, further comprising determining whether there are correlations between clinical or laboratory characteristics, associated with each assigned location, and the different biological analyses.

13. The method of claim 1, wherein the biological sample is a tissue specimen or cellular preparation.

Sub A6> 14. The method of claim 12, wherein the clinical and laboratory characteristics are determined apart from performing the different biological analysis of each copy of the array; and

the characteristics are one or more of patient age, tumor grade, tumor size, node status, and receptor status.

15. The method of claim 1, wherein placing the specimen in an assigned location in the array comprises placing a sample in a corresponding position of multiple copies of an array.

Sub A7> 16. A method of parallel analysis of identical arrays of tissue specimens, comprising:

forming a donor block comprising a biological specimen embedded in embedding medium;

obtaining a plurality of elongated donor sample cores from the biological specimen;

boring receptacle cores from a recipient embedding medium to form an array of elongated receptacles;

placing the donor sample cores in the elongated receptacles at assigned locations in the array;

sectioning the recipient embedding medium transverse to the elongated receptacles to obtain a cross-section of the donor sample cores in the array, while maintaining the assigned locations in the array in consecutive cross-sections;

performing a different biological analysis of each cross-section; and

comparing a result of each biological analysis in corresponding assigned locations of different sections to determine if there are correlations between the results of the different biological analyses at each assigned location.

17. The method of claim 16, further comprising comparing the results of the different biological analyses at each assigned location to clinical information about the biological specimen at the assigned location.

18. The method of claim 17, wherein the biological specimen is a tissue specimen from a tumor.

19. The method of claim 17, wherein the biological analyses are selected from the group consisting of a histologic analysis, an immunologic analysis, and a nucleic acid hybridization analysis.

20. The method of claim 17, wherein the results of the different biological analyses are compared to clinical information obtained about a subject from whom the biological specimen was obtained.

21. The method of claim 16, further comprising aligning a thin tissue section above the donor block to identify an area of interest from which the donor sample core is taken.

22. The method of claim 16, wherein the elongated donor sample core is a substantially cylindrical core that has a diameter that is less than about 1 mm.

Sub A8) 23. A cross-section of the donor sample cores obtained by the method of claim 14.

23 24. The method of claim 1, further comprising using a nucleic acid microarray to identify a biomarker to be used in a biological analysis on the recipient array.

Cont'd Sub A9) 25. The method of claim 24, wherein the nucleic acid array is a cDNA or oligonucleotide microarray.

25 26. The method of claim 24, wherein the biomarker is selected by a high throughput immunological or genetic analysis.

26 27. The method of claim 24, wherein the biomarker comprises a marker for gene expression.

27 28. The method of claim 26, wherein the biomarker comprises a structural or numerical alteration of a chromosome, chromosomal region, gene, gene fragment or locus, or a gene function alteration.

28 29. The method of claim 1, wherein comparing the results comprises determining if there is an alteration of a gene by examining a marker for protein expression or other gene alteration.

29 30. The method of claim 28, wherein the alteration of protein expression is determined by an immunologic analysis.

30 31. The method of claim 28, wherein the alteration is an overexpression of vimentin in renal cell carcinoma, or an overexpression of IGFBP2 in human prostate cancer, or an overexpression of PDGFB in breast, lung, colon, testicular, endometrial or bladder cancer.

Cont'd 31 32. A method of analyzing genetic changes or gene expression in a tissue specimen, comprising:

screening multiple genes in a biological specimen, with a nucleic acid array that detects which genes are abnormally expressed in the biological specimen; and

screening multiple biological specimens in a biological specimen array, with a nucleic acid probe to detect which genes are abnormally expressed in the biological specimens;

wherein the result of screening multiple genes is used to select the nucleic acid probe to screen the multiple biological specimens, or wherein the result of screening multiple tissue specimens is used to select the array that detects which genes are abnormally expressed.

32 33. The method of claim 31, wherein screening multiple genes comprises performing a high throughput genomic technique.

33 ~~34~~. The method of claim ~~32~~ 31, wherein the high throughput genomic technique is selected from the group of cDNA or genomic DNA sequencing, protein sequencing, RDA, differential display, subtractive hybridization, SAGE, hybridization based sequencing, and cDNA and oligonucleotide arrays.

34 ~~35~~. The method of claim ~~32~~ 31, wherein screening multiple genes to determine which genes are abnormally expressed comprises searching databases and other biomedical sources of information.

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35 ~~36~~. The method of claim ~~32~~ 31, wherein screening the multiple genes comprises using a cDNA array to determine which genes are abnormally expressed.

36 ~~37~~. The method of claim ~~32~~ 31, wherein screening the multiple genes comprises providing a DNA array which is assayed for a gene amplification, deletion, mutation, polymorphism, methylation change or other alteration of gene structure or function, or a genetic or molecular marker that reflects this change.

37 ~~38~~. The method of claim ~~37~~ 36, wherein the DNA array is a microarray that contains target loci that undergo differential expression in cancer.

38 ~~39~~. The method of claim ~~32~~ 31, wherein screening multiple genes obtained from a single biological specimen comprises hybridizing nucleic acid molecules associated with a cell with the DNA array that contains target loci that undergo differential expression, and determining which target loci indicate differential expression of a gene in the cell.

39 ~~40~~. The method of claim ~~39~~ 38, further comprising selecting a target locus that undergoes differential expression, providing a probe that includes or is complementary to at least a portion of the target locus, and using the probe to screen the multiple biological specimens.

40 ~~41~~. The method of claim ~~32~~ 31, wherein the biological specimen is a tissue specimen.

41 ~~42~~. The method of claim ~~41~~ 40, wherein the tissue specimen is a tumor specimen.

Sub A10 43. The method of claim 1, wherein the results of the different biological analyses are used to:

a. evaluate a reagent for disease diagnosis or treatment;

b. identify a prognostic marker for a disease;

c. prioritize targets for drug development;

d. assess or select therapy for a disease type; or

e. find a biochemical target for medical therapy.

A3 ~~44~~. The method of claim ~~43~~ 42, wherein evaluating a reagent for disease diagnosis or treatment comprises evaluating a reagent selected from the group of antibodies, genetic probes, and antisense molecules.

45. The method of claim 44, wherein evaluating a reagent for disease diagnosis or treatment comprises evaluating a reagent selected from the group of biological inhibitors, biological enhancers, or other biological modulators.

46. The method of claim 43, wherein identifying a prognostic marker for cancer comprises selecting a marker associated with a poor clinical outcome.

47. The method of claim 43, wherein selecting therapy for the subject comprises selecting an antineoplastic therapy that is associated with a particular biological analysis outcome.

48. The method of claim 47, wherein the particular biological analysis outcome is an oncogene amplification, deletion, translocation, mutation or other genetic rearrangement which is correlated with a clinical response to a particular therapy.

49. The method of claim 1, wherein the donor specimens are specimens from one or more tumors.

50. The method of claim 49, wherein the donor specimens are specimens from one or more tumors selected from the group of breast, prostate and bladder cancer.

51. The method of claim 49, wherein the donor specimens are specimens from a plurality of tumors all of the same organ or histologic type.

52. The method of claim 48, wherein the donor specimens are specimens from a plurality of tumors from different organs or tissue types.

53. A method of constructing a specimen array, comprising:

providing cellular specimens in a matrix, with the specimens positioned at predetermined known positions, such that when multiple copies of the matrix are provided, a two dimensional array of specimens is presented on each copy, with each specimen at a predetermined position in the matrix, and wherein each matrix has a third dimension so that when sequential copies of the matrix are provided, the specimens maintain a predetermined relationship in the array; and

exposing sequential copies of the matrix to an agent which interacts with the specimens of the array, to identify those specimens which share a common biological property.

54. The method of claim 53, wherein the specimens are provided in an elongated form, and multiple copies of the matrix are made by cutting sections from a three dimensional array into predetermined sections, such that as sequential sections of the matrix are cut, the specimens maintain the predetermined relationship.

55. The method of claim 53, wherein the common biological property is a morphologic or molecular characteristic.

56. The method of claim 53, wherein the common biological property is a presence or absence, or altered level of expression, of a gene or protein, alteration of copy number, structure or function of a gene, genetic locus, chromosomal region or chromosome.

57. The method of claim 54, wherein the common biological property is a specific reaction with an antibody specific for a specimen of interest.

58. The method of claim 53, wherein the common biological property is correlated with an other characteristic of the specimens.

59. The method of claim 58, wherein the other characteristic of the specimens includes clinical information about a subject from whom each specimen was taken.

60. The method of claim 59, wherein the clinical information includes one or more of clinical course, treatment response, histological type or grade, tumor stage, age and sex of the subject from whom each specimen was taken.

61. The method of claim 53, wherein the cellular specimen is a tissue specimen.

62. The method of claim 53, wherein the cellular specimen is a cellular suspension.

63. The method of claim 62, wherein the specimen is a liquid cellular specimen that has been converted into a solid cellular specimen.

64. The array of claim 53.

65. The array of claim 54.

66. The method of claim 53, further comprising exposing a gene array to a candidate specimen, and selecting a candidate probe for the specimen array.

67. The method of claim 53, wherein the common biological property is her-2 status, and the method further comprises selecting a therapy based on her-2 status.

68. The method of claim 63, wherein the specimens comprise a tissue from a model or transgenic organism.

69. The method of claim 68, wherein the specimens comprise tissue from the model or transgenic organism at different stages of development.

70. The method of claim 53, wherein the specimens comprise animal, yeast or bacterial cells.

71. The method of claim 70, wherein the cells are in a liquid suspension which is applied to a surface of a support.

72. The method of claim 71, wherein the liquid suspension is from a body fluid.

73. The method of claim 72, wherein the body fluid is selected from the group of a needle aspiration, a cytology specimen, urine, and ascitic fluid.

74. The method of claim 70, wherein the cells comprise a sample of a liquid malignancy.

75. The method of claim 74, wherein the liquid malignancy comprises a hematological malignancy.

76. The method of claim 70, wherein the cells are from one or more cell lines.

76 77. The method of claim 53, wherein the specimens comprise specimens from one or more tumors at different stages of progression.

77 78. The method of claim 77, wherein the one or more tumors are prostate cancer tumors.

79. A method of screening for cancer in a specimen, comprising determining whether platelet derived growth factor beta (PDGFB), FGFR2, MYBL2,or IGFBP2 is expressed, overexpressed or amplified in the specimen.

80. A method of screening for cancer in a specimen, comprising determining:

whether PDGFB is overexpressed or amplified in the specimen, wherein the cancer is selected from the group of lung, bladder and endometrial cancer;

whether FGFR2 is amplified in the specimen, wherein the cancer is breast cancer;

whether IGFBP2 is expressed in the specimen, wherein the cancer is hormone refractory prostate cancer;

whether MYBL2 is amplified and expressed in breast cancer; and

whether MYC, AR and cyclin-D1 are amplified in prostate cancer.

81. The method of claim 80, wherein the method comprises determining whether PDGFB is overexpressed or amplified in the specimen, wherein the cancer is selected from the group of lung, bladder and endometrial cancer.

82. The method of claim 80, wherein the method comprises determining whether FGFR2 is amplified in the specimen, wherein the cancer is breast cancer.

83. The method of claim 80, comprising determining whether IGFBP2 is expressed in the specimen, wherein the cancer is hormone refractory prostate cancer.

84. The method of claim 80, comprising determining whether MYBL2 is amplified and expressed in breast cancer.

85. The method of claim 80, comprising determining whether MYC, AR and cyclin-P1 are amplified in prostate cancer.

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